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NEW FORMS OF EVERGREENING IN AUSTRALIA: MISLEADING ADVERTISING, ENANTIOMERS AND DATA EXCLUSIVITY: APOTEX v SERVIER AND ALPHAPHARM v LUNDBECK

Two recent decisions of the Federal Court of Australia have provided interesting insights into the ongoing struggle between originator drug manufacturers and the public interest in Australia. In Apotex Pty Ltd (formerly GenRx Pty Ltd) v Les Laboratoires Servier (No 2) [2008] FCA 607 the court held that an advertising campaign by an originator pharmaceutical company, which sought to persuade doctors to issue prescriptions prohibiting substitution of "a-flagged" generics, constituted misleading and deceptive conduct under s 52 of the Trade Practices Act 1974 (Cth). The decision of the court in Alphapharm Pty Ltd v H Lundbeck A/S (2008) 76 IPR 618; [2008] FCA 559 limits the ability of the manufacturer of a drug based on a purified racemate enantiomer to claim a later registration date on the Australian Register of Therapeutic Goods and subsequently obtain an extension of its intellectual monopoly privileges as well as an exclusivity period for the data it had submitted to safety regulators. Importantly, this case is one of the first to consider recent allegedly pro- and anti-"evergreening" changes to the Therapeutic Goods Act 1989 (Cth) and Patents Act 1990 (Cth) as impacted by the intellectual property chapter (Ch 17) of the Australia–United States Free Trade Agreement.

BACKGROUND

The generics industry in Australia has recently gone through considerable regulatory and industrial change.[1] A recent survey by PriceWaterhouseCoopers of pharma companies revealed that two thirds of respondents have considered withdrawing products from the Australian market if shifting from the F1 (patent protected) to F2 (generic) category with mandatory price cuts results in their products falling below international benchmarks.[2] An aspect of the same concern will be that Australian drug companies will be keen to preserve F1 status for their drugs as long as possible through legal and marketing strategies, consequently weakening generic competition. As such, it is instructive to consider two recent Australian cases that have involved generic pharmaceuticals: *Apotex Pty Ltd (formerly GenRx Pty Ltd) v Les Laboratoires Servier (No 2)* [2008] FCA 607 (*Apotex v Servier*)and *Alphapharm Pty Ltd v H Lundbeck A/S* (2008) 76 IPR 618; [2008] FCA 559 (*Alphapharm v Lundbeck*). The respective clinical and then general regulatory backgrounds to these decisions need to be explained first Since 1992 Servier has been the patent-holder and marketer of Coversyl, containing perindopril as its active pharmaceutical ingredient (API). This drug is a treatment for hypertension, heart failure and the risk of myocardial infarction in patients with established coronary artery disease; perindopril blocks the activity of angiotensin-converting enzyme (ACE). Coversyl is the most prescribed ACE inhibitor on the Australian Pharmaceutical Benefits Scheme (PBS) with approximately 360,000 patients regularly taking this medication. After the original patent expired, the rival company GenRx distributed in Australia a generic form of the perindopril erbumine salt.

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[1] Faunce TA, "Challenges for Australia's Bio/Nanopharma Policies: Trade Deals, Public Goods and Reference Pricing in Sustainable Industrial Renewal" (2007) 4 Aust New Zealand Health Policy 9.

[2] Anon, "Low Price PBS Products Face Chop", *Pharma in Focus* (1-7 Sept 2008).

Before Servier's main patent for perindopril expired, however, Servier had substituted an equivalent salt form (perindopril arginine) for the same clinical indications as its original perindopril erbumine salt formulation and sought to de-list the older form of the drug from the PBS ("the salt switch"). Because hypertension requires a long-term daily treatment regime, repeat prescriptions are required and patient compliance becomes a major issue. Whether the new Servier perindopril should be preferred over the older Servier drug form, against which the GenRx generic version (certified as bioequivalent on safety, quality and efficacy grounds by the Therapeutic Goods Administration (TGA)) was "a-flagged" in PBS listings, led to controversial clinical and marketing consequences. This provided the direct clinical and regulatory background to *Apotex v Servier*.

Alphapharm v Lundbeck concerned the antidepressant citalopram. Depression, and in particular, major depressive disorder (MDD) is a common psychiatric disorder. Its basis is thought to be a disruption of normal neural transmission. Serotonin (5-HT) is a neurotransmitter which allows messages to be transmitted between nerves. As serotonin was comparatively deficient in MDD sufferers, it was thought that if the reuptake of 5-HT by nerve cells could be inhibited, there would be more free 5-HT in the synapses between the nerve cells, and that this would improve neurotransmission and therefore give relief from MDD. This was the intellectual background that led to the development of the class of antidepressants known as selective serotonin (5-HT) reuptake inhibitors (SSRIs), the term "selective" implying the avoidance of undesirable side-effects.

Fluoxetine (sold under the brand name "Prozac"), paroxetine (marketed under the brand name "Seroxat"), and citalopram were early SSRIs. Fluoxetine and citalopram were racemates and paroxetine was a single enantiomer. Citalopram was considered to be the most selective of these SSRIs. When Lundbeck's citalopram patent was set to expire, Lundbeck sought to patent the purified enantiomer of its active pharmaceutical ingredient and to obtain a patent-term extension for delayed marketing approval.[3] Both of these tactics would have kept out of the market the generic form of the drug manufactured by Alphapharm.

In all jurisdictions, any new therapeutic drug must first be approved for safety, quality and efficacy before it may be lawfully marketed and supplied.[4] In Australia, the task of regulating and approving new drugs is handled by the TGA.[5] Once approved by the TGA, the new therapeutic drug is listed, along with details of any particular patient conditions and doses, on the Australian Register of Therapeutic Goods (ARTG).[6] Following this initial registration, the new drug can subsequently seek listing on the PBS,[7] whereby it is listed by its brand name, at a pre-determined price and specified dose.

Registration costs for listing a new patented prescription drug on the ARTG are modest (approximately A$176,000, compared to A$67,300 for a generic product) in relation to the considerable responsibility placed upon the safety, quality and efficacy investigation process.[8] Patent terms of 20 years for pharmaceutical products[9] are subject to a further extension of up to five years to

[3] Under the *Patents Act 1990* (Cth), s 70.

[4] The *Therapeutic Goods Act 1989* (Cth), s 19B, creates a range of criminal offences prohibiting the importation or export, supply or manufacture of a therapeutic drug without approval or exemption from the TGA. Civil penalties are set out at s 19D of the Act.

[5] *Therapeutic Goods Act 1989* (Cth); *Therapeutic Goods Amendment (Medical Devices) Act 2002* (Cth); *Therapeutic Goods (Charges) Act 1991* (Cth).

[6] *Therapeutic Goods Act 1989* (Cth), Ch 2.

[7] The PBS is administered under the *National Health Act 1953* (Cth); for some proposed modifications to the way new drugs are submitted to the Pharmaceutical Benefits Advisory Committee (PBAC) see the *National Health Amendment (Pharmaceutical and Other Benefits – Cost Recovery) Bill 2008* (Cth) (referred to Senate Committee, 18 July 2008); *National Health Amendment (Pharmaceutical Benefits Scheme) Bill 2008* (Cth).

[8] Therapeutic Goods Administration, *Summary of Fees and Charges at July 1 2008* (Australian Department of Health and Ageing), http://www.tga.gov.au/fees/fees08.htm viewed 16 July 2008.

[9] *Patents Act 1990* (Cth), s 67.

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compensate for delayed registration approval.[10] This leads to Australian patent extinguishment often being delayed compared to United States and European jurisdictions for the same product. Section 25A of the *Therapeutic Goods Act 1989* (Cth) also requires "protected information", provided to drug regulatory authorities to permit safety, quality and efficacy investigations, to remain confidential for a period of five years after the granting of a patent.[11]

"Evergreening" is a term that refers to the variety of strategic methods by which an originator company protects the royalties flowing from an original patent over an active pharmaceutical substance. As a commercial strategy it can involve threats to licensing arrangements with and even buyouts of generic companies or their products. Technical "evergreening" often sees the creation of process, use or incremental innovation patents over, among other things, new methods of drug delivery or dosage; alleged innovations that themselves are often of dubious novelty, inventiveness or community value.[12] Article 17.10.4 of the *Australia–United States Free Trade Agreement* (hereafter AUSFTA)[13] represented a significant facilitation in the brand name drug manufacturers' "evergreening" capacity. For the first time in Australia it required linkage of the approval process of a drug safety, quality and efficacy regulator (the TGA) with the supervision of drug patent status. It required the establishment of a process (by amendments to the *Therapeutic Goods Act*) whereby an originator manufacturer had to be informed of planned generic entry to the market.[14] Alphapharm had to make such a notification to Lundbeck.

Generic drug manufacturers in Australia have recently been subject to another challenge. After minimal parliamentary scrutiny, the *National Health Amendment (Pharmaceutical Benefits Scheme) Act 2007* (Cth) was passed in August 2007, amending key provisions of the *National Health Act 1953* (Cth). The legislation effectively created two PBS pricing formularies: "F1", comprising single brand, mostly patented and "innovative" drugs, and "F2", comprising multiple brand, mostly generic medicines. Reference pricing in some forms no longer occurs between the two formularies, diminishing the extent to which the PBS processes now can be said to be based on scientific valuing of a therapeutic drug's objectively demonstrated therapeutic significance.[15]

APOTEX V SERVIER: FACTS AND BASIC ISSUES

As the Federal Court explained in *Apotex v Servier* (at [5]):

> Where a particular drug is listed on the PBS by an originator company, a supplier of another brand of that drug may apply to have its brand listed on the PBS as a substitute. In order to be substitutable, the applicant must demonstrate that the new brand has the same active ingredient as the listed brand and is bioequivalent within acceptable levels identified in a particular standard. The existence of substitutable brands for a particular brand of drug is known as "a"-flagging and is indicated by the letter "a" immediately before the brand name of the drug in the PBS schedule.

With its 1992 patent for perindopril erbumine set to expire in 2002, Servier substituted an "equivalent salt form", perindopril arginine, in a move the court described (at [13]) as "the salt switch". The active ingredient remained the same. Servier then sought to "de-list" the older salt formulation from the ARTG (at [17]), which, it was alleged by GenRx, could have affected the "a"-flagging status of GenRx's generic equivalent. While GenRx alleged that Servier's conduct was motivated more by commercial interests (that is, it was an "evergreening" tactic) rather than "clinical

[10] *Patents Act 1990* (Cth), s 77(1), (2).

[11] Inserted by the *Therapeutic Goods Legislation Amendment Act 1998* (Cth) Amending Act (No 34, 1998), and s 70 of the *Patents Act* was inserted in 1998 under the *Intellectual Property Laws Amendment Act 1998* (No 100, 1998), with a technical amendment made in 2005 by the *Statue Revision Act* (No 100, 2005).

[12] For an exploration of evergreening in an Australian context see Chalmers R, "Evergreen or Deciduous? Australian Trends in Relation to the 'Evergreening' of Patents" (2006) 30 MULR 29; Faunce TA and Lexchin J, "'Linkage' Pharmaceutical Evergreening in Canada and Australia" (2007) 4(1) *Australian and New Zealand Journal of Health Policy* 8.

[13] Signed 18 May 2004, 2005 ATS 1 (entered into force 1 January 2005).

[14] Faunce TA, "Reference Pricing for Pharmaceuticals: Is the Australia–United States Free Trade Agreement Affecting Australia's Pharmaceutical Benefits Scheme?" (2007) 187(4) MJA 240.

[15] Faunce TA and Lofgren H, "Drug Price Reforms: The New F1–F2 Bifurcation" (2007) 30 *Australian Prescriber* 138.

rationale" (at [17]), the new salt did have an improved shelf-life and product stability over the older erbumine salt and GenRx's alternative (at [18]). Ultimately however, the move by Servier was unsuccessful, as the PBS maintained GenRx's product's "a"-flag status as substitutable for both the "old" Coversyl and the "new" perindopril arginine Corversyl despite the different shelf-lives of the products (at [17]).

Importantly for GenRx, the court continued, stating (at [17]):

> A drug may be "a"-flagged as substitutable for a listed PBS drug with different "finished product" stability, meaning different shelf life or storage conditions.

Salt switches are among the technical methods used by pharmaceutical companies to "evergreen" the royalties flowing from a soon-to-expire patent over an API.[16] In this instance, GenRx saw Servier's motive for the salt switch in its product as an attempt to eliminate GenRx's potential to have its generic clinically substituted and prescribed in place of Corversyl. The court noted (at [62]) that, while many generic drugs are cheaper than an originator's version, both Corversyl and GenRx's alternative are sold to the patient at the same price.

Under the *National Health Act 1953* (Cth), a doctor is given discretion over whether to allow generic substitution or not. The court referred (at [6]) to s 103(2)(A) of the *National Health Act* which allows for substitution where:

> (a) the person who prescribed the specified benefit did not indicate on the prescription that only that benefit was to be supplied; and
> (b) the Schedule of Pharmaceutical Benefits issued by the Department states that the specified benefit and the substitute benefit are equivalent; and
> (c) the substitute benefit is a listed brand of a pharmaceutical item; and
> (d) the supply of the substitute benefit is not prohibited by a law of the State or Territory in which the substitute benefit is supplied.

The court in *Apotex v Servier* added (at [7]):

> The decision to allow generic substitution … is in the unfettered discretion of the prescribing doctor. There are no other detailed regulations or guidelines directing that discretion. Once the doctor indicates that there is to be no substitution, a pharmacist must dispense the prescribed drug and may not substitute [another].

The reasons are many and varied why doctors do not allow pharmacists to substitute a cheaper generic product that has been proved to be bioequivalent on safety, quality and efficacy grounds with a brand name product (at [63]):

- the doctor has formed the view that brand substitution causes patient confusion which can lead to non-compliance with treatment, particularly in the elderly;
- substitution is made by the pharmacist without the doctor having the opportunity to counsel the patient about a change in formulation;
- not permitting brand substitution minimises the variables for patients on treatment regimes involving a number of different medications;
- lack of familiarity with a brand, tablet appearance, dosage and packaging of a medication may negatively affect patient compliance and consistency of treatment, particularly in patients who are elderly, cognitively impaired, on multiple medications or where the medication is for the treatment of chronic conditions;
- the need for simplicity and consistency of treatment to minimise confusion that could result in non-compliance;
- the adverse effect on the patient level of compliance, the level of the patient's adherence to and persistence with the medication regime prescribed;
- some reports indicate some generic formulations may be of inferior pharmaceutical quality;
- the importance of supporting companies that undertake research and development which is the source of new medications; and
- the doctor and patient support given by the originator company.

[16] Chalmers, n 12 at 33.

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The "no brand substitution" stamp and direct-to-patient advertising

Exploiting the discretion over brand substitution afforded to doctors in the legislation, Servier began a targeted advertising campaign, which the court ultimately found to be misleading and deceptive, in breach of s 52 of the *Trade Practices Act*. The campaign consisted of a stamp, distributed to some 3,000 doctors, and four advertisements "placed in medical publications" which made (at [52]), GenRx alleged, the following assertions:

1. Brand substitution not permitted for COVERSYL.
2. αBrand substitution not permitted for COVERSYL.
3. Brand substitution for New COVERSYL is never permissible.
4. There are no other perindopril products substitutable with New COVERSYL.

While the use of the *Trade Practices Act* to deter an attempt to undermine generic alternatives is a novel "anti-evergreening" approach, the decision in *Apotex v Servier* highlights the difficulties which must be overcome by a plaintiff. First, the group targeted by the representation must be established (at [56]).[17] If it is not the community at large, then the sub-groups must be identified, whose constituent members may be less likely to be deceived or misled by the conduct complained of. In *Apotex v Servier* the court determined that Servier's stamp and advertising were directed to doctors, pharmacists and patients currently taking Coversyl.

The court found that doctors would not have been misled by the stamp, stating (at [66]):

> The ordinary and reasonable doctor would not be misled by the printed text of the stamp. He or she would not be led to believe that it meant that there was some regulatory inhibition on brand substitution. If the doctor thought that there was no permitted substitution or some regulatory proscription on substitution, there would be no need to use the stamp.

However, the court found (at [81]) that a pharmacist, when confronted with a doctor's prescription affix with the "No Substitution" stamp issued by Servier, could be misled or deceived into thinking that there existed a blanket prohibition on substitution for Coversyl. Relying on the testimony of two pharmacists, the court held (at [79]) that it was enough that a pharmacist "laboured under an erroneous assumption as to the substitutability of new Coversyl" which was neither "extreme [nor] fanciful" for it to find the stamp deceptive and misleading.

The court rejected Servier's contention that there existed "no basis" for assuming that a "hypothetical ordinary or reasonable patient will come to a view about a subject matter relating to his or her own treatment without obtaining some understanding about that matter from his or her doctor or pharmacist" (at [82]). In doing so, the court accepted the testimony of an expert witness for Servier, who conceded that a not insignificant proportion of patients may become confused as to whether generic substitution is prohibited and "may or may not" have that confusion resolved by their treating doctor (at [85]). The court found (at [86]) that the stamp was likely to mislead patients who were prescribed perindopril.

The findings of the court suggest that pharmaceutical advertising which targets doctors alone is less likely to attract a judicial finding of misleading or deceptive conduct than where it also aims to influence pharmacists and patients. Spending on direct-to-patient advertising (DTPA) is only a small proportion of all advertising expenditure by global pharmaceutical firms, if United States trends are representative. Pharmaceutical advertising spending in the United States "rose from $11.4 billion in 1996 to $29.9 billion in 2005", although DTPA "made up only 14% of total promotional expenditures in 2005".[18] Unbranded direct-to-consumer marketing campaigns, labelled "disease awareness campaigns", are effective in stimulating product-specific sales.[19]

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[17] Quoting *Campomar Sociedad, Limitada v Nike International Ltd* (2000) 202 CLR 45.

[18] Donohue J, Cevasco M and Rosenthal M, "A Decade of Direct-to-Consumer Advertising of Prescription Drugs" (2007) 357 NEJM 673. Some academics continue to substitute "consumer" for "patient" in this context, highlighting their vulnerability to corporate branding and merchandising of pharmacoregulatory concepts.

[19] 't Jong GW, Stricker BHC and Sturkenboom MCJM, "Marketing in the Lay Media and Prescriptions of Terbinafine in Primary Care: Dutch Cohort Study" (2004) 328 BMJ 931.

Currently the *Therapeutic Goods Act 1989* (Cth) contains a prohibition on DTPA for prescription and pharmacist-only medicines which limits the exposure of companies to allegations of misleading or deceptive conduct.[20] This legislation is in accordance with the *National Strategy for the Quality Use of Medicines* and the *National Medicines Policy* in terms of responsible advertising and information dissemination.[21] The *National Competition Review of Drugs, Poisons and Controlled Substances Legislation* (the Galbally report) in 2001 recognised the importance of this legislation in its purpose to prevent the economic, social and health costs of DTPA.[22] The internet is an exception whose role in DTPA has been enhanced as a result of a provision in Annex 2C of AUSFTA to allow "information dissemination" to "health professionals and consumers".

Use of the internet for DTPA may be caught by prohibitions in the *Trade Practices Act 1974* (Cth) but the AUSFTA provision may lead to lobbying by Medicines Australia of any Australian government that attempted to enforce such prohibitions or attempted to restrict industry attempts to directly influence patients.

The Australian ban on DTPA is supported by the *Therapeutic Goods Advertising Code*, administered by the Therapeutic Goods Advertising Commission. Advertising of prescription medicines is controlled under an industry self-regulation Code and system administered by Medicines Australia, the industry lobby group representing the manufacturers of patented prescription pharmaceutical products. The Code, however, allows companies to run marketing campaigns for consumers which masquerade as disease awareness campaigns. The Code's regulatory process also relies on complaints made by the public and during the lengthy process of investigations the advertising campaign in question is not required to be withdrawn, allowing ample opportunity for its message to reach the public regardless of the outcome of these investigations. For example, following a complaint about an advertising campaign for Levitra(r), a drug marketed for erectile dysfunction, Medicines Australia's Code of Conduct Committee found that the use of a company logo or common graphical elements with health professional advertising should not be regarded necessarily as DTPA involving link to a specific product.[23]

In *Apotex v Servier* liability attached to Servier from its "No Substitution" stamp campaign chiefly because the representations did not just influence the treating doctor but continued through to the patient and pharmacist. Although the stamp was a novel and almost unique strategy, Servier's "No Substitution" slogan may have escaped condemnation if it had been solely directed at the treating doctors in the more traditional flyer form.[24]

Pharmaceutical advertisements in medical journals

Servier also placed four advertisements in medical journals which, GenRx pleaded, made the representation that new Coversyl had "improved stability" over perindopril erbumine (at [102]), among other claims. GenRx alleged that these advertisements, in general terms, conveyed express or implied representations which included the following in relation to new Coversyl:

1. that brand substitution was not permitted;
2. that there were no other perindopril products on the market that could substitute for it;

[20] *Therapeutic Goods Act 1989* (Cth), s 42DL(1)(f).

[21] Australian Government, Department of Health and Ageing, *National Medicines Policy*, http://www.health.gov.au/internet/main/publishing.nsf/Content/National%20Medicines%20Policy-2 viewed 11 September 2008.

[22] Galbally R, *National Competition Review of Drugs, Poisons and Controlled Substances Legislation Final Report Part A; Section 5.1 Advertising* (Council of Australian Governments, 2001) p 50.

[23] Medicines Australia Code of Conduct Committee, *Code of Conduct Complaints Relating To Activities Directed at the General Public* (January-December 2006), http://www.medicinesaustralia.com.au/pages/images/Code%20of%20Conduct%20activities%20directed%20at%20the%20general%20public%20Jan-Dec%202006.pdf viewed 11 September 2008.

[24] See, for comparison, the court's discussion of *AstraZeneca Pty Ltd v GlaxoSmithKline Australia Pty Ltd* [2006] ATPR 42-106; [2005] FCA 1645 in *Apotex Pty Ltd (formerly GenRx Pty Ltd) v Les Laboratoires Servier (No 2)* [2008] FCA 607 at [110].

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3. that investing in Australia and investing profits in research were relevant to doctor's choice about substitutability of new coversyl,
4. that patient and doctor support was relevant to substitutability of new coversyl,
5. that improved stability and shelf life is relevant to substitutability of new coversyl.

While the court dismissed the majority of GenRx's complaints, holding Servier's advertisements as not likely to mislead or deceive medical practitioners (at [111]-[112]), it distinguished the claim of "improved stability", as it "assert[ed] a clinical benefit" (at [113]). The court, accepting testimony from both a doctor and a pharmacist, determined that as Coversyl and its generic substitutes are commonly prescribed drugs, unlikely to be stocked for more than 12 months, the "improved stability" claimed by Servier was, clinically, a "non-benefit" (at [119]).

This raises important considerations for manufactures of pharmaceuticals. In finding that an advertised "non-benefit", although "literally true",[25] can still be misleading and deceptive, the court has raised the standard required by advertising to more than just truthfulness. Following *Apotex v Servier*, companies seeking to market their medication should ensure that any claims as to new benefits are relevant to a "clinical purpose" (at [119]), or "regulatory decisions" (at [114]), and do not simply remedy problems whose significance is merely "speculative" or hypothetical (at [118]).

Clearly, manufacturers have a duty to their shareholders to responsibly promote their product after a patent has expired, if it has community value. Such efforts, however, should draw short of "evergreening" strategies which are primarily designed merely to maintain their market dominance. The actions of Servier, first in attempting to "delist" old Coversyl from the ARTG, and then attempting to influence a doctor's discretion against allowing generic substitution, appear chiefly motivated by the same spirit as patent "evergreening": to restrict or deny the entry of a competitor into a market once held fast under a patent monopoly. While the Australian Government considers doctors, rather than patients, to be the more appropriate target of pharmaceutical advertising, the actions of Servier highlight the extent to which advertising may mislead or confuse even those who stand at the ethical and regulatory centre of the medical profession.

ALPHAPHARM V LUNDBECK: FACTS AND BASIC ISSUES

The active pharmaceutical ingredient citalopram was first given regulatory safety approval as an antidepressant in 1989 in the United States and was first registered on the ARTG in Australia in 1997, under the trade mark Cipramil. Citalopram is a molecule used in the treatment of depression and contains a racemate mixture of two enantiomers (+)-citalopram and (-)-citalopram. Subsequent testing, after the priority date, revealed that pure (+)-citalopram was therapeutically more active than citalopram itself, and more than 100 fold more active than (-)-citalopram.

In 1989 H Lundbeck A/S (Lundbeck), a Danish pharmaceutical company, was granted a patent over the "(+)-enantiomer of citalopram and process for the preparation thereof" by the Australian Patent Office (at [3]). In September 2003 the TGA listed Lundbeck's new anti-depressant Lexapro on the ARTG. Lexapro contained escitalopram the purified (+)-citalopram enantiomer.

Alphapharm Pty Ltd v H Lundbeck A/S (2008) 76 IPR 618; [2008] FCA 559 concerned a challenge by Alphapharm, a generic pharmaceutical manufacturer, against the Lundbeck patent over the purified racemate escitalopram. Alphapharm argued, among other things, that the original citalopram patented API contained escitalopram (albeit in an unpurified form) and that, therefore, the 1989 patent failed for obviousness or lack of novelty.

On 15 June 2005, Alphapharm sponsored an application to the TGA for approval to market and sell a product containing (+)-citalopram (manufactured by a certain method described in certain specified documents) and for that purpose provided the TGA with certificates pursuant to s 26B(1)(a) of the *Therapeutic Goods Act 1989* (Cth). This amendment had been inserted by the *US Free Trade Implementation Act 2004* (Cth), Sch 7 and has been alleged by some commentators to facilitate the

[25] To use the GenRx's language: *Apotex Pty Ltd (formerly GenRx Pty Ltd) v Les Laboratoires Servier (No 2)* [2008] FCA 607 at [113].

process known as "linkage evergreening".[26] The accompanying letter stated:

> Subject to obtaining the requisite regulatory approvals and listings, it is Alphapharm's desire to engage in the following activities (none of which have commenced) in relation to Escitalopram Oxalate Goods for the Australian market:
>
> (i) manufacture at Carole Park;
> (ii) offer for sale;
> (iii) sell;
> (iv) otherwise dispose of;
> (v) use; and
> (vi) keep for the purpose of doing any of those things.
>
> Alphapharm does not presently intend importing Escitalopram Oxalate Goods into Australia or exporting Escitalopram Oxalate Goods (other than perhaps for regulatory purposes) from Australia.
>
> (4) Alphapharm has not manufactured and does not intend manufacturing the active pharmaceutical ingredient escitalopram oxalate ("API") used in its Escitalopram Oxalate Goods. Alphapharm has imported and intends in the future importing API … in the form of tablets for the Australian market …
>
> (5) The intermediate used by Alphapharm's API supplier in the process of manufacturing the API is (+/-)-4-bromo-alpha[1]-(4-fluorophenol)-alpha[1]-[3-(dimethylamino)propyl]-1,2-benzene dimethanol hydrobromide [not] 4-(4-dimethylamino)-1-(4'-flourophenyl)-1-(hydroxyl-1-butyl)-3-(hydroxymethyl)benzonitrile as claimed in claim 6 of the Patent.

Section 26B of the *Therapeutic Goods Act*, referred to above, requires that in certain circumstances an applicant to the TGA for registration or listing of therapeutic goods must provide to the TGA (s 26B(1)(a)):

> A certificate to the effect that the applicant, acting in good faith, believes on reasonable grounds that it is not marketing and does not propose to market, the therapeutic goods in a manner, or in circumstances, that would infringe a valid claim of a patent that has been granted in relation to the therapeutic goods;

Expert evidence disclosed that separating the enantiomers of citalopram was difficult in the 1980s and Alphapharm was unable to challenge the Lundbeck patent for the method the latter had developed. Obviousness was a more difficult issue. Alphapharm argued that since it was known that at least one of the two citalopram enantiomers would function as an SSRI in treating depression, then it must be obvious to create a purified form of one of them. *Alphapharm v Lundbeck* was, in the court's opinion, the first Australian case where a patent "relating to a single enantiomer" product had been challenged on the grounds of obviousness (at [175]).

Alphapharm supported its arguments on "obviousness" by relying on evidence touching the pharmaceutical drug, thalidomide. This showed that there was an established scientific interest in resolving racemates into their enantiomers and a desire on the part of pharmaceutical companies to do so (at [396]-[401]). Thalidomide was a pharmaceutical drug, administered as a racemate, which had been prescribed for treating morning sickness in pregnant women. In the early 1960s the drug was reported to cause birth defects in babies and, as a result of that disaster, stricter drug testing was introduced. It was later discovered that one enantiomer of the drug was safe while the other caused teratogenic effects (that is to say, damaged the embryo). As a consequence, the isolation of single enantiomers became an increasingly significant research focus around the world, and the possibility that different enantiomers might behave differently in the human body became an issue of major concern to drug developers.

The court pointed (at [176]) to the discussion of the High Court in the development and history of "obviousness" in *Lockwood Security Products Pty Ltd v Doric Products Pty Ltd (No 2)* (2007) 81 ALJR 1070 at [38]-[49] as it related to patent law in Australia. What is obvious for these purposes is assessed from the perspective of a "non-inventive skilled addressee or team in the field of the invention" and looks to "what was known" at the time (at [178]).[27] Under the *Patents Act 1952* (Cth),

[26] Faunce and Lexchin, n 12.

[27] Quoting *Aktiebolaget Hässle v Alphapharm Pty Ltd* (2002) 212 CLR 411.

"common general knowledge" did not include publications unless "their content was part of the common knowledge at the priority date" (at [179]). In *Aktiebolaget Hässle v Alphapharm Pty Ltd* (2002) 212 CLR 411 the High Court put forward the proposition that the issue of "obviousness" was to be determined by considering if the hypothetical non-inventive skilled addressee "would have 'as a matter of routine' taken steps towards the invention".[28] "Obviousness", as such, was to be decided on two points: first, whether the hypothetical non-inventive skilled addressee would have been led, "'as a matter of routine' to the desired result"; and, secondly, if there was "a reasonable expectation of achieving that result" (at [180]).

Ultimately, the court held (at [409]) that, in 1988, it was scientifically difficult and so not common to resolve such a racemate into its separate enantiomers. Further, as citalopram was a "highly selective SSRI with no evidence of toxicity" (at [389]), there would be less motivation for a company to seek to resolve citalopram into its constituent enantiomers.

For these reasons, the court found that making a purified enantiomer of citalopram was not an obvious goal and so the product claims were valid.

Patent extension for delayed marketing approval

Lundbeck had submitted an application for a patent extension as compensation for delayed regulator safety, quality and efficacy approval under s 70 of the *Patents Act 1990* (Cth) for escitalopram. This was granted, with the effect that Lundbeck's patent would expire in June 2014 rather than June 2009. Alphapharm argued that the Commissioner for Patents had acted incorrectly in granting Lundbeck's request as the application for patent extension had been made out of time.

Under the *Patents Act*, a new pharmaceutical product can be granted a 20-year patent,[29] which begins from the date the complete patent specifications were filed.[30] As this date is usually well before the TGA begins to assess the product for listing on the ARTG, a patentee is able to apply for an extension of up to five years to compensate them for any regulatory delay.[31]

Section 70 of the *Patents Act* provides:

> (1) The patentee of a standard patent may apply to the Commissioner for an extension of the term of the patent if the requirements set out in subsections (2), (3) and (4) are satisfied.
> (2) Either or both of the following conditions must be satisfied:
> (a) one or more pharmaceutical substances per se must in substance be disclosed in the complete specification of the patent and in substance fall within the scope of the claim or claims of that specification;
> (b) …
> (3) Both of the following conditions must be satisfied in relation to at least one of those pharmaceutical substances:
> (a) goods containing, or consisting of, the substance must be included in the Australian Register of Therapeutic Goods;
> (b) the period beginning on the date of the patent and ending on the first regulatory approval date for the substance must be at least 5 years.
> (4) …
> (5) For the purposes of this section, the first regulatory approval date, in relation to a pharmaceutical substance, is:
> (a) if no pre-TGA marketing approval was given in relation to the substance [none was given in the present case] – the date of commencement of the first inclusion in the Australian Register of Therapeutic Goods of goods that contain, or consist of, the substance; or

This non-use-related patent extension for up to five years for delayed pharmaceutical marketing approval was "locked-in" by the AUSFTA, Art 17.9.8(b).[32] Article 17.9.8(b) of the AUSFTA

[28] Quoting *Aktiebolaget Hässle v Alphapharm Pty Ltd* (2002) 212 CLR 411.

[29] *Patents Act 1990* (Cth), s 67.

[30] *Patents Act 1990* (Cth), s 65.

[31] *Patents Act 1990* (Cth), s 70.

[32] *Patents Act 1990* (Cth), ss 70-79A (Div 2 of Pt 3 of Ch 6).

provided:

> (b) With respect to a pharmaceutical product that is subject to a patent, each Party shall make available an adjustment of the patent term to compensate the patent owner for unreasonable curtailment of the effective patent term as a result of the marketing approval process.

The period between the grant of the initial patent and its "first regulatory approval date" must be "at least five years".[33] The regulatory approval date is the first of either the product's listing on the ARTG or the date of any "pre-TGA marketing approval".[34] Fatally, as it turned out for Lundbeck, an application for a patent extension under Ch 6, Pt 3 must be made within six months after the date of commencement of the first inclusion in the Australian Register of Therapeutic Goods of goods that contain, or consist of, any of the pharmaceutical substances referred to in s 70(3).[35]

As the court pointed out (at [22]):

> Underlying these provisions are certain assumptions. One is that it may be unreasonable to expect a patentee to derive a sufficient return from a pharmaceutical patent within 20 years because of the necessity, under the TG Act, of first having the relevant goods listed on the ARTG, and of the time that it may take to obtain that listing. Another assumption, however, is that the patentee should not be permitted to "sit on its hands" once the patent has been issued and once the relevant goods have been listed on the ARTG.

The argument before the court was whether the "first approval date" for escitalopram was September 2003 – when Lexapro (containing unpurified escitalopram) was listed on the ARTG – or December 1997 – when Cipramil (containing purified escitalopram) was listed on the ARTG.

The court dismissed Lundbeck's arguments that the purified racemate contained a new pharmaceutical substance "per se" with a different therapeutic effect as the Act required, stating (at [512]):

> [T]he therapeutic benefit of citalopram comes from the presence in it of (+)-citalopram. It would not be right to say that Cipramil does not contain (+)-citalopram merely because the therapeutic effect of the racemate is less effective because of the additional presence in it of (-)-citalopram.[36]

Ultimately, the court held that the Lundbeck's application under s 70 of the *Patents Act* had been made outside of the six-month period stipulated by s 71(2) and that the patent extension was therefore invalid.

Data exclusivity

Alphapharm invited the TGA, when evaluating its application for an abbreviated process register for its bioequvalent generic on the ARTG, to rely on the data that had been filed by Lundbeck Australia's application to register Lexapro, including clinical studies, patient data and expert reports. Section 25A of the *Therapeutic Goods Act* protects information divulged to the TGA for safety, quality and efficacy evaluation for a period of five years except with the permission of the registration holder.[37] Such information could otherwise be used by a generic producer to prepare for market launch upon patent expiry ("springboarding"). This data exclusivity protection is an additional protection to those incorporated in the World Trade Organisation *Trade-Related Intellectual Property Rights* (TRIPS) agreement. It was the subject of Art 17.10.1(a) of the AUSFTA which required the Australian Government to pass legislation preventing marketing approval of a generic (regardless of a competitor's patent expiry) within five years of the competitor's submission to regulatory authorities of undisclosed test data about safety or efficacy. Such a provision cuts across the fundamental understanding that the intellectual monopoly privilege conferred by a patent is designed to encourage the free distribution of knowledge.

[33] *Patents Act 1990* (Cth), s 70(3)(b).

[34] *Patents Act 1990* (Cth), s 70(5)(a), (b).

[35] *Patents Act 1990* (Cth), s 71(2)(b).

[36] *Therapeutic Goods Act 1989* (Cth), s 70(2)(a).

[37] *Therapeutic Goods Act 1989* (Cth), s 25A(e), (f).

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The question here for the court was whether information provided by Lundbeck Australia to the TGA in support of its application for the registration of Lexapro was protected information for the purposes of s 25A(1). Section 25A provides:

> (1) When evaluating therapeutic goods for registration, the Secretary must not use information about other therapeutic goods that is protected information.
> (2) Information is protected information if:
> (a) the information was given to the Secretary in relation to an application to register therapeutic goods (the new goods):
> (i) not being therapeutic devices; and
> (ii) consisting of, or containing, an active component; and
> (b) the information is about the active component and is not available to the public; and
> (c) when the application to register the new goods was lodged:
> (i) no other therapeutic goods consisting of, or containing, that active component were included in the Register; and
> (ii) no such therapeutic goods had been included in the Register at any time before then; and
> (d) the new goods became registered on or after the commencement of this subsection; and
> (e) 5 years have not passed since the day the new goods became registered; and
> (f) the person in relation to whom the new goods are registered has not given the Secretary permission in writing for the Secretary to use the information.
> (3) For the purposes of subsection (2), an active component, in relation to therapeutic goods, is a substance that is, or one of the substances that together are, primarily responsible for the biological or other effect identifying the goods as therapeutic goods.
> (4) The use of protected information contrary to subsection (1) does not render the Commonwealth, the Secretary or a delegate of the Secretary liable to a person in respect of loss, damage or injury of any kind suffered by the person as a result of, or arising out of, the use of that information.

This raised four specific issues:

- Was Cipramil (citalopram hydrobromide) another therapeutic good "consisting of, or containing" (+)-citalopram within the meaning of s 25A(2)(c)(i)?
- What was the "information" that Lundbeck Australia contends is protected?
- Was that information "about" the enantiomer (+)-citalopram for the purposes of s 25A(2)(b)?
- Was that information "available to the public" within the meaning of s 25A(2)(b)?

The court held that only information relating to a new therapeutic good which subsequently becomes registered on the ARTG is "protected".[38] The court also found (at [548]) that Lundbeck's claim for data exclusivity over either all or some unidentified part of the information that Lundbeck provided to the TGA in seeking to register Lexapro was "far too wide" and that s 25A(2) defines "protected information" in a far more limited way.

Springboarding during the patent extension period

Lindgren J noted that s 78(2) was repealed on 25 October 2006 by the *Intellectual Property Laws Amendment Act 2006* (Cth). That amending Act also inserted s 119A into the Act to cover any exploitation on or after 25 October 2006. Section 119A is wider than s 78(2). According to the Explanatory Memorandum, the purpose of the amendment was to "allow springboarding as an exception to patent infringement on any pharmaceutical patent at any time for purposes solely in connection with gaining regulatory approval of a pharmaceutical product in Australia or another territory" (at [643]). Section 119A applies even where no extension of the term of the patent has been granted (at [643]). "Springboarding" refers to the capacity of a generic manufacturer to use scientific data lodged with a regulatory agency by a drug patent holder to develop a product which will be available to market immediately the primary patent ceases. Strategies that inhibit "springboarding" are likel to represent "evergreening" and have a deleterious impact on the affordability of medicines. From a public health point of view, access to affordable medicines will be facilitated if applications for or actual extensions of the standard patent term do not inhibit "springboarding" by generic competitors.

[38] *Therapeutic Goods Act 1989* (Cth), s 25A(c), (d)

IMPROVING THE PLACE OF GENERICS IN THE AUSTRALIAN REGULATORY SYSTEM

In 2002 an extensive and lengthy inquiry by the United States Federal Trade Commission (FTC) found that as many as 75% of new drug applications by generic drug manufacturers suffered legal actions under patent laws by the original brand name patent owner.[39] These were driving up United States drug costs by keeping the cheaper generic versions off the market. The FTC recommended that only one injunction against a potential generic market entrant be permitted per product.[40] This change was implemented when the United States legislature passed its *Medicare Prescription Drug Improvement and Modernisation Act 2003* (US), creating in s 1101 a complicated process of early declaratory relief.

With the creation of new F1 (single brand, mostly patented) and F2 (multiple brand) categories in the PBS, the latter subject to compulsory price cuts, the issue of "evergreening" will loom large as companies try to stave off competition and keep their products in the F1 PBS category. Although "evergreening" encompasses a wide variety of tactics, the two cases discussed here show a new range of tactics that may be employed:

- potentially misleading or deceptive advertising;
- patent extensions for delayed regulatory approval (in the absence of criteria requiring that the manufacturer did not itself prolong the regulatory process);
- data exclusivity claims; and
- patent claims over incremental product modifications with marginal obviousness.

Alphapharm v Lundbeck highlights the importance of data exclusivity as an evergreening strategy in Australia.[41] The capacity of generic companies to rely on originator quality, safety and efficacy data to prepare for market launch ("springboarding") is an important right recognised by the TRIPS agreement.[42] Data exclusivity is not mentioned in TRIPS, but is a so-called TRIPS-plus (TRIPS-minus from a public health point of view) requirement.

Anti-evergreening provisions were introduced into s 26 of the *Therapeutic Goods Act* at the time of AUSFTA implementation as a clear sign that the Australian Government had a legitimate expectation that none of the provisions therein would facilitate "evergreening" of drug patents in Australia. This is consistent with Art 27 of TRIPS which permits specific legislation dealing with a problem that only arises in one industry sector (such as "evergreening" in relation to the pharmaceutical sector). The United States has disagreed.[43]

Australia's *Patents Act* was recently amended to ensure "springboarding" protection for intending generic market entrants. Patent extensions for delayed marketing approval may undermine this important public interest capacity unless they are linked to criteria requiring proof that the applicant did not contribute to the regulatory delay through inadequate production of data or some other delaying tactic. Annex 2C.1 of the AUSFTA makes clear that the operation of "competitive markets" is one way in which pharmaceutical innovation can be rewarded in the respective countries. This creates a need for much greater involvement of anti-trust and competition regulators in monitoring and shaping the activities of the pharmaceutical industry in Australia.

Australian patent law should carefully circumscribe data exclusivity monopolistic protections, particularly if they start to erode generic "springboarding" capability. Just as intellectual monopoly

[39] Federal Trade Commission, *Generic Drug Entry Prior to Patent Expiration: An FTC Study* (United States Federal Trade Commission, 2002).

[40] Glasgow L, "Stretching the Limits of Intellectual Property Rights: Has the Pharmaceutical Industry Gone Too Far?" (2001-2002) 41 *Journal of Law and Technology* 227.

[41] Teuten A, *Strategies for Extending the Period of Exclusivity of a Pharmaceutical Product* (Sagittarius Intellectual Property Consultants), http://www.sagittariusipc.co.uk/AT_presentation_Jan04.pdf viewed July 2005.

[42] *Agreement on Trade-Related Aspects of Intellectual Property Rights* (*TRIPS*) 1995 ATS 38 (entered into force 1 January 1995).

[43] See item 6 (Pharmaceutical Patents) of Department of Foreign Affairs and Trade, *Letter from Robert Zoellick to Mark Vaile, 18 May 2004* (Australian Department of Foreign Affairs and Trade), http://www.dfat.gov.au/trade/negotiations/us_fta/final-text/letters/ip_zoellick_vaile.pdf viewed July 2005; Pharma in Focus, *US Still Watchful on FTA* (Pharma in Focus Subscription Service), http://www.pharmainfocus.com.au/news.asp?newsid=517 viewed 12 September 2005.

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privilege periods associated with patents have a corresponding public interest trade off in the distribution of knowledge, so should data exclusivity periods. They should not interfere with the capacity to compulsorily license recently patented medicines in national emergencies, or to satisfy the needs of developing countries which lack pharmaceutical manufacturing capacity.

An amendment to s 101 of the *National Health Act 1953* (Cth) now requires the Pharmaceutical Benefits Advisory Committee (PBAC) (s 101(3BA)) to specify in a listing recommendation to the Minister whether the drug or medicinal preparation and another drug or medicinal preparation should be treated as interchangeable on an individual patient basis. The latter phrase may well be a robustly objective concept in the PBS lexicon, but it certainly does not appear as scientifically rigorous as "bioequivalence". Its misuse could constitute yet another "evergreening" strategy.

To encourage a generic pharmaceutical industry in Australia, it is critical that more legislative encouragement be given to the first generic player willing to take on the patent thicket created by the originator company. A process for rapidly sorting out patent claims and a dedicated pharmaceutical patent register facilitating patent searching would be positive regulatory contributions. Generic companies have to do a lot of innovative research and development in order to get around the originator patent thickets. Greater assistance should be provided to generic manufactures so as to encourage their entry into the marketplace as the viability of the generics industry is of benefit to both government and citizenry.

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